ANIMAL
HEALTH
INSTITUTE

Representing manufacturers of animal health products

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President & CEO

August 23, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Docket No. 99D-2406 – International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH); Draft Guideline on VICH Topic GL9 Good Clinical Practices

The **ANIMAL HEALTH INSTITUTE** ("AHI") submits these comments in response to the Notice of availability and request for comments published by the Food and Drug Administration in the Federal Register on Tuesday, August 3, 1999, regarding the Draft Guideline on Good Clinical Practices, VICH Topic GL9.

AHI is the national trade association representing manufacturers of animal health products – the pharmaceuticals, vaccines and feed additives used in modern food production, and the medicines that keep livestock and pets healthy.

The Food and Drug Administration should be applauded for embracing the International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) process and entering into harmonization discussions with other regulatory authorities. In today's increasingly global market, harmonization of technical requirements for product registration is critical to the continued vitality of the domestic and global animal health markets. Increased efficiency and cost savings realized through harmonization of technical requirements for product registration will benefit the public and the food producer through increased numbers and availability of veterinary medicinal products.

AHI has been actively involved in the VICH process, and has already had significant input into the VICH GL9 (GCP) document released by the VICH Steering Committee in October 1998 for consultation at Step 4 of the VICH process. The document referenced by FDA in the Federal Register is similar to, but not identical to, the VICH document. As a whole, AHI is very pleased with the draft document and believes, with minor comment, that the document is sound and should be adopted by FDA. Specific comments are set forth below. Where AHI believes a

99D-2406

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**I. References to Legal Liability**

**1.24 Sponsor**
An individual company, institution or organization which takes responsibility for the initiation, management, and financing of a clinical study ~~and is liable~~ for the veterinary product under investigation.

**4.1. General.** An individual, company, institution or organization which takes responsibility for the initiation, management, and financing of a clinical study ~~and is liable~~ for the veterinary product under investigation.

Sections 1.24 and 4.1 provide definitions and general information, respectively, about sponsors. Each of these sections includes language regarding legal liability. Such language has no place in this guideline. The purpose of VICH is to provide for the harmonization of **technical** requirements for registration and licensure of veterinary medicinal products among the participating regulatory authorities. The stated purpose does **not** involve creating or fixing **legal** liability. The phrase "and is liable" should be deleted from both sections. Deletion of these phrases does not alter the meaning or description provided in the sections in any manner. The fact that their deletion doesn't alter the meaning or intent of the sections strongly mitigates in favor of their exclusion from the final document. There are already numerous aspects of domestic and foreign law that create potential legal liability for a product sponsor. In the current litigious society, there is simply no justifiable reason for the inclusion of notions of legal liability in a technical document.

**III. should**

**3.2.13** Obtain informed consent from each owner, or owner's agent, before their animal(s) participate in the study. Each owner or owner's agent <u>should</u> receive relevant information regarding such participation from the investigator prior to giving their consent.

**4.2.7** Sign, along with the investigator, the study protocol as an agreement that the clinical study will be conducted according to the study protocol. Any amendments to the study protocol <u>should</u> have the signed agreement of both sponsor and investigator.

**8.1.2** All study documentation should be retained for the period of time required by the required by relevant regulatory authorities. Any or all of the study documentation described in this guidance is subject to, and should be available for monitoring on behalf of the sponsor. Study documentation should be audited by

the sponsor's quality audit procedures, consistent with well-recognized and accepted principles of quality assurance. When a quality audit is conducted, the author should prepare a report for the sponsor which details the auditing process and which certifies that the audit has been conducted.

**8.4.1** All study documentation should be stored in a manner that protects it from deterioration, destruction, tampering or vandalism in accordance with the nature of the records. The storage site should permit the orderly storage and easy retrieval of the retained documentation.

The FDA version utilizes the language "should" at Sections 3.2.13, 4.2.7, 8.1.2 and 8.4.1. The VICH GL9 (GCP) draft utilizes the language "must" in these locations. AHI supports these changes. Use of the discretionary "should" over the mandatory "must" provides for better regulatory flexibility to meet individual circumstance.

## IV. Definitions

**1.1 Adverse Event (AE)**
Any harmful and unintended ~~abnormal~~ response associated with the use of a veterinary product or investigational veterinary product, whether or not considered to be product related.

**1.15 Investigational Veterinary Product**
Any biological or pharmaceutical form of, or any animal feed containing one or more active substances being evaluated in a clinical study, to investigate any protective, therapeutic, diagnostic, or physiological effect when administered or applied to an animal.

The definition of "Adverse Event" in § 1.1 should be consistent with the definition used in the VICH Pharmacovigilance Guideline. At its March 1999 meeting, the VICH Pharmacovigilance working group agreed that the definition of "Adverse Event" involves any harmful and unintended observation after the use of a veterinary medicinal product. Use of the concept of "harmful and unintended" should be utilized over "abnormal" because, depending on the circumstances, an abnormal observation in an animal following administration of a veterinary medicinal product may be intended and/or expected. This is especially true with clinical trials involving diseased animals. AHI urges FDA to change the definition in § 1.1 as set forth above, and to utilize the same definition for "Adverse Event" across the board.

Section 1.15 provides a definition for "Investigational Veterinary Product." However, the definition does not include biologicals. Section 1.31 defines "Veterinary Product" and includes biologicals. To be consistent, AHI recommends Section 1.15 be amended to include the above-indicated language.

## V. THE PRINCIPLES OF VICH GCP

1.7 Wherever possible, investigational veterinary products should be prepared, handled and stored in accordance with the concepts of good manufacturing practice (GMP) of the relevant regulatory authority. Details of preparation, handling and storage of investigational veterinary products should be documented and the products used in accordance with the study protocol.

For the sake of clarification, we recommend the addition of the phrase "of the relevant regulatory authority" at the end of the first sentence of § 2.7. Because there are differences among the GMPs of the various regulatory authorities, the addition of this phrase indicates that the GMP to be utilized is the one where the sponsor intends to market the product.

## VI. Investigator Responsibilities

3.2.6 Notify the sponsor ~~immediately~~ promptly of any study protocol deviation.

In section 3.2.6 an investigator is required to notify the sponsor immediately of any deviation. "Immediately" is a term that has different definitions to different individuals. An insignificant deviation may not require after-hours notification. Replacing "immediately" with "promptly" allows for some flexibility and, yet, still suggests notification sooner rather than later. Additionally, use of the term "promptly" is consistent with § 3.2.16 which requires investigators to "promptly notify the sponsor of adverse events."

## VII. Sponsor Responsibilities

4.2.11 Ensure the proper final and safe disposal of all study animals and any edible products derived from them according to the study protocol.

AHI recommends the inclusion of the phrase "according to the study protocol" at the end of the sentence in § 4.2.11. The added language clarifies the sponsor's responsibility. The sponsor is to follow the animal according to the study protocol. "Final and safe disposal" seems to indicate following the animal through death and disposal. This may or may not be appropriate for any given study. For example, in a companion animal study treating patients recruited from veterinary practices with naturally occurring disease, the animal may not die for years following the conclusion of the study. It would be inappropriate to require sponsors to follow such an animal through death and disposal.

**VIII. The Monitor**

**5.1 General.** An individual appointed by the sponsor or CRO to be responsible to the sponsor or CRO for monitoring and reporting on the progress of the study, verifying the data and confirming that the clinical study is conducted, recorded and reported in compliance with GCP and applicable regulatory requirements. The monitor should have scientific training and experience to knowledgeably oversee a particular study. The monitor should be trained in quality control techniques ~~and data auditing procedures~~. The monitor should understand all applicable protocol requirements and be able to determine whether the study was conducted in accordance with the protocol. An individual should not serve as both the monitor and investigator for any one study. The monitor is the principal communication link between the sponsor and the investigator.

**5.2.7** Not, in any way, bias or be part of ~~the record-keeping or~~ the data collection process, other than to ensure that the current study protocol, GCP and applicable regulatory requirements are being followed.

The deletion of the phrase "and data auditing procedures" from the description of a monitor in § 5.1 will provide for flexibility. Data auditing is a quality assurance function. While it is certainly not inappropriate for a monitor to be trained in data auditing procedures, it is not required. In fact, in many studies the functions of the monitor and quality assurance are separated, with different individuals performing monitoring and quality assurance functions.

In § 5.2.7 deletion of "the record-keeping or" is needed for clarification. AHI agrees that a monitor should not collect raw data. However, it is common for monitors to clerically draft some of the documents signed by the investigator. The monitor does not create the information, but simply transcribes it into the appropriate format. Investigators are often busy, and this helps ensure that documents are completed timely, accurately, and appropriately. The monitor does not bias the study and is not part of the record-keeping process for raw data, but could be said to generate some of a study's records. This is consistent with the intent of the section.

**IX. Study Protocol**

**6.3.20.1** List any study specific technical SOPs that apply to ~~the~~ conducting~~,~~ ~~monitoring and reporting of~~ the study.

Section 6.3.20.1 should be amended to include the above-indicated language that limits the appended SOPs to those related to the technical performance of the study. Many firms have developed voluminous internal SOPs regarding the conduction of studies in general. Such internal SOPs are not specific to any particular study. To require appending these SOPs to a study protocol will unnecessarily and considerably increase the size of the study protocol.

Limiting this section to appending SOPs related to the technical aspects of the study comports with the intent of the section.

**X. The Final Study Report**

**7.3.6.4** Animal disposal. A summary ~~complete description~~ of the disposal of the study animals and their edible products.

**7.3.6.5.5** A summary ~~Full inventory~~ of use and disposal of all investigational veterinary product and control product(s) shipped or delivered to the investigator.

**7.3.9.1** Handling of records.

Both § 7.3.6.4 and § 7.3.6.5.5 should be changed, as set forth above, to require only a summary of the disposal of study animals and a summary of the use and disposal of investigational and control products. Details of both will certainly be available for inspection and auditing should a regulatory authority desire. However, the inclusion of detail on these topics is not needed in the Final Study Report. A summary of the information with the ability to review the detail if needed should suffice.

With respect to §7.3.9.1, AHI seeks clarification of the intent and meaning of this section. Another section covers the location of study documentation. "Handling of records" is vague and subject to varying interpretations. We believe the intent of the section should be ascertained and more descriptive language be utilized.

**XI. Study Documentation**

**8.1.3** Any or all of the study documentation described in this guidance may be inspected, audited and copied by the relevant regulatory authority as part of the process to confirm the validity of the study conduct and the integrity of the data collected. Any copies of study documentation should be formally submitted to the appropriate regulatory authority with assurances for tracing the documents and ensuring the protection of confidential business information.

AHI urges the inclusion of the additional sentence, set forth above, to § 8.1.3. This language is necessary to protect sponsor's confidential business information. AHI agrees that the regulatory authority should be able to copy study documentation. Formal submission of copies will help maintain the security of the documentation and protect confidential business information. If an inspector is allowed to arrive on-site and copy documentation, there is less assurance of security and the protection of confidential business information.

## XII. Typographical Errors

The following typographical errors were noted during review of the document.

A. In § 1.31 the word "effect" should be "affect."

B. In § 2.2 the document has "the -integrity." No hyphen is indicated.

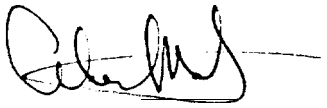
C. In § 4.2.8 the numbering of the subsections is incorrect.

D. In § 5.1 in the second to last sentence, the FDA document has "anyone," and the VICH GL9 version has "any one." The "any one" version is correct.

E. In § 7.2.1.2 the word "the" should be inserted before the abbreviation "FSR."

AHI is pleased to provide these comments to FDA regarding the Draft Guidelines on Good Clinical Practices, VICH Topic GL9.

Sincerely,



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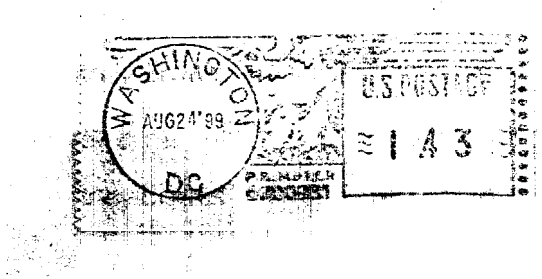


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